REMARKS/ARGUMENTS

Claims 24-40 are pending and stand rejected in this application.

Applicants thank the Examiner for acknowledging the correction of inventorship and making the appropriate changes. Applicants respectfully request reconsideration of the rejected claims in view of the arguments made below.

Claim Rejections Under 35 USC § 103(a)

Claims 24, 29, and 38-40 were rejected under USC § 103(a) as allegedly being unpatentable over Zonana et al. (U.S. Patent 6,355,782) in view of Dong et al. (U.S. Patent 6,361,947). Specifically, the office action asserts that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Zonana with the detection method of Dong.

Specifically, with regards to Claim 29, it was stated that Zonana discloses the use of PCR products as driver.

With regards to Claims 38 and 39, it was stated that Zonana discloses a driver with a biotin tag that binds to streptavidin magnetic beads.

Claim 40 was similarly rejected over the alleged disclosure in Zonana for the separation of a subset of complementary tester nucleic acids from the subset of immobilized complementary driver nucleic acids using the biotin streptavidin interaction.

Applicants respectfully traverse all of the above rejections.

Response to Examiner's Rebuttal of Applicant's Arguments

Applicants respectfully submit that the instant invention is not obvious in light of the prior art for the reasons previously presented, as well as those that follow.

In the rebuttal to Applicant's prior arguments that were presented in the correspondence filed on October 14, 2003, the Examiner alleges that there was "abundant motivation" to combine the teachings of Zonana with Dong and further, that such a combination would render

the claimed invention obvious. In reaching the above conclusion, the Examiner first alleges that Zonana uses an array by equating a "gridded plate" used to grow the bacterial clones containing the cloned selected cDNA to an array ("In fact, the cDNAs were actually placed into an array, the gridded plates...."). Applicants point out that a gridded plate as described by Zonana is by no means the same as a "nucleic acid probe array" as taught by the present invention. Specifically, one of skill would not equate a nucleic acid probe array that comprises probes on a substrate with a plate used to grow bacterial colonies, gridded or not. Even if the gridded plates of Zonana were equivalent to the nucleic acid probe array of the present invention, the present invention as claimed could not be practiced on the gridded plates since the present invention comprises "hybridizing said subset of complementary tester nucleic acids to probes on a nucleic acid probe array" and the gridded plates have neither probes nor the ability to be hybridized to the subset of complementary tester nucleic acids.

Further, Examiner states that "Zonana expressly indicates that this placement is made to permit further analysis". Actually, what Zonana states is that "Bacteria were grown on gridded plates *prior to* further analysis" [emphasis added] and that "One of the clones, cDS 446, was used for further analysis." Applicants can find no instance where Zonana states that the placement on the gridded plates is made to "permit" further analysis and respectfully requests that the Examiner indicate where in Zonana this is suggested. In addition, Examiner indicates that the placement permits further analyses, including "DNA sequencing (see column 24), expression analysis (see column 26), haplotype analysis (see column 39), as well as an express suggestion for the use of DNA chips for mutation detection at column 54, lines 5-9." Applicants respectfully disagree with the Examiner's assertion that plating the bacterial clones on gridded plates permits these further means of analysis. The gridded plates were simply used as a means of growing individual bacterial colonies containing the cloned selected cDNAs, only one of which was used for further analysis.

Examiner states that "an ordinary practitioner would have been motivated by Dong to use an array in the place of the more cumbersome cloning methods used by Zonana for further analysis since Dong expressly teaches that array detection is a preferred method of analysis of the isolated subsets." However, Applicants strongly believe that there would be no motivation for

one of skill to combine the references of Zonana and Dong to arrive at the instant invention. In order to practice the method of Zonana using an array as taught in Dong, one would first need to know the sequence of the nucleic acid entity that one wants to identify. Zonana performed a cDNA selection methodology involving tester and driver nucleic acids as a means to isolate a *dl* cDNA fragment, but the actual sequence of that fragment was not yet known to Zonana. Put another way, although Zonana did know the *identity* of the cDNA selected by the tester-driver method (a fragment of the *dl* cDNA), Zonana did not know the *sequence* of that cDNA, as evidenced by the fact that following the selection the cDNA was cloned and used to identify a full-length cDNA from a cDNA library that was then sequenced. If the sequence of that cDNA had been known, the sequencing step would have been unnecessary. In addition, the disclosure of Zonana states that the DNA sequences of the *dl* cDNAs are "provided by this invention", further emphasizing that these sequences were unknown prior to the sequencing by Zonana. (column 3, lines 46-53). As such, a nucleic acid probe array containing probes that would hybridize to the selected cDNA could not have been designed since the sequence of the cDNA selected using the tester-driver method of Zonana was unknown. Therefore, at best the combination of Zonana's tester-driver method with Dong's array would have resulted in a nucleic acid probe array containing no probes.

Applicants recognize that Zonana desired to further analyze the cDNA selected by the tester-driver method, but contend that this could not have been done by nucleic acid probe array since the sequence of this selected cDNA was unknown until sequencing was performed. Array analysis after sequencing would be pointless since the existence and sequence of the cDNA would already be known so there would be nothing to gain by this type of analysis. The other means of further analyzing the cDNA were performed after cloning, screening a cDNA library, PCR amplification and sequencing. These methods included northern analysis, Southern analysis, whole mount *in situ* hybridization, and expression analysis. In none of these methods is the use of nucleic acid probe arrays mentioned or suggested. Although Zonana may, as alleged, describe the use of DNA chips for mutation detection, there is no suggestion that the tester-driver method be used to prepare a sample for use on a nucleic acid probe array, as is taught in the present invention. Rather, the method suggested by Zonana is simply for "detecting mutations in the

genes", *i.e.* in the genes of the protein ligand (EDA1-II) and receptors (dl and DL) involved in ectodermal dysplasia, the sequences of which are disclosed by Zonana. Nowhere in the description of these diagnostic applications is any mention of the tester-driver method nor the applicability of this method for use with nucleic acid probe arrays.

In view of the foregoing, Applicants submit that in addition to a lack of motivation to combine, the combination of Zonana with Dong would not result in an operable invention, and certainly not the invention as claimed by the instant claims. Although Examiner alleges that there is "abundant motivation" to combine the references of Zonana and Dong, Applicants submit that the alleged motivation to combine Zonana and Dong is clearly founded on a lack of understanding of the methods practiced in the cited art. As no advantage would result from the combination of the tester-driver method of Zonana with the array method of Dong, there can be no motivation to combine these methods. Accordingly, the Applicants believe that the instant invention is patentable over the cited references and respectfully request that the rejection of claims 24, 29, and 38-40 be withdrawn.

Claims 25-28, 30 and 32-37 were rejected under USC § 103(a) as allegedly being unpatentable over Zonana et al. (U.S. Patent 6,355,782) in view of Dong et al. (U.S. Patent 6,361,947) as applied to claims 24, 29, and 38-40 and further in view of Wigler et al. (U.S. Patent 5,501,964). Applicants respectfully traverse the instant rejection.

Applicants submit that Zonana and Dong fail to teach the presently claimed invention as set forth above. To attempt to overcome deficiencies in these references, the Examiner relies on Wigler et al., alleging that each of the dependent claims mentioned above were rendered obvious by the teachings of Wigler. Applicants submit that nothing in Wigler corrects the deficiencies of the combination of Zonana with Dong.

Wigler is allegedly directed at comparing DNA from two sources wherein the DNA may be cDNA, genomic DNA, etc. Zonana's method is directed at separating a fragment of *dl* cDNA from a mixture of cDNA fragments, cloning that fragment, and using that cloned fragment to screen a cDNA library to isolate a cloned, full-length *dl* cDNA. As noted above, an ordinary practitioner would not be motivated to combine Dong's detection method with Zonana for achieving the desired result of Zonana's method. Combining Wigler with the teachings of

Zonana and Dong does not remedy the deficiencies of Zonana and Dong. As such, the cited references fail to render the claimed invention obvious. Hence, the Applicants respectfully request that the Examiner withdraw the instant rejection.

Conclusion

In view of the foregoing remarks, Applicants believe that the present application is in condition for allowance and action towards that end is respectfully requested. If the Examiner believes that a telephone interview would expedite the examination of this application, the Examiner is requested to contact the undersigned at the telephone number provided.

Respectfully submitted,

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